

# CARDIOVASCULAR DISTURBANCES CAUSED BY DEFICIENCY OF VITAMIN B<sub>1</sub>

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Deficiency of vitamin B<sub>1</sub> causes two distinct sets of signs and symptoms, affecting either the cardiovascular system or the nervous system. In their extreme forms these conditions constitute "wet" and "dry" beri-beri. Although both systems are commonly affected, it is usual for one to dominate the clinical picture. Beri-beri is still a frequent cause of illness and death in China, Japan, the Philippine Islands, the East Indies, and Brazil; in the last few years attention has been drawn to its occurrence in the United States of America. In England gross deficiency of vitamin B<sub>1</sub> is rare, but mild and sub-clinical states are probably fairly common.

The studies of Wenckebach (1934) upon so-called "beri-beri heart" in Java and of Keefer (1930) in China have been admirably extended by Soma Weiss and his colleagues; in Boston cardiovascular disturbances, due probably to deficiency of vitamin B<sub>1</sub>, are not uncommon; they occurred in a ratio of about 1 in 160 admissions to the medical wards, and were more frequent than congenital heart disease or subacute bacterial endocarditis (Weiss and Wilkins, 1937). Few cases have been reported in this country. One of us described two cases of cardiovascular disturbances associated with low blood vitamin B<sub>1</sub> to the Association of Physicians in 1938 (Sinclair, 1938), and nine cases more recently (Sinclair, 1939, c). Six cases with heart failure or œdema and significantly low values for vitamin B<sub>1</sub> diphosphate ester in the blood have also been reported (Goodhart and Sinclair, 1940). Price (1938) recorded a case of wet beri-beri associated with chronic alcoholism and a deficient diet, and Garrett (1938) a case of "polyneuritis with œdema simulating beri-beri" which he did not believe to be due to a vitamin deficiency. Yudkin (1938) described a case of wet beri-beri in an Indian living in London on a diet mainly of rice; no vitamin B<sub>1</sub> was found in his urine before treatment. Wood (1939) has discussed two cases; Jones and Bramwell (1939) have recently described a case of "alcoholic beri-beri" responding to treatment with vitamin B<sub>1</sub>; and Boyd Campbell and Allison (1940) have reported a case of beri-beri (polyneuritis and changes in the electrocardiogram) combined with pellagra in Belfast.

The following three cases are reported because they were diagnosed as wet beri-beri on clinical grounds, and responded well to therapy with vitamin B<sub>1</sub>; two of them gave very low values of this vitamin in the blood before treatment, but in the third this was not estimated.

#### CASE 1. BERI-BERI IN A CHRONIC ALCOHOLIC

A florist, aged 39, was admitted to hospital on September 9, 1936. His first symptoms, 15 months previously, were pains in the legs and numbness of the feet. Bilateral foot drop then developed, and for one year he could only walk with sticks. Six months before admission swelling of the legs and shortness of breath added to his troubles, but he continued at work, serving in his shop until August. The shortness of breath was then evident even at rest, and cough disturbed his sleep.

For 17 years he had drunk about six pints of beer or stout daily. His appetite, though never large, had begun to fail in recent weeks.

On examination he was of a ruddy complexion with slight cyanosis of the lips. Tense œdema extended half way up the thighs and round the sacrum. Orthopnœa was urgent, and the cervical veins were engorged up to the angle of the jaw in the sitting position.

The brachial and radial arteries felt normal for his age, and no changes were visible in the retinal arteries. The blood pressure was 135/80 mm. The pulse was regular and the rate 120. The apex beat was felt three quarters of an inch external to the left nipple line. The heart sounds were tic-tac in quality, and no murmurs were heard.

The respirations were 23 per minute, and coarse rales were heard over both lung bases. The liver was tender and extended down to the umbilicus. Both grips, and flexion and extension of the elbows, were weak. There was bilateral foot-drop and tenderness of the calves. The knee and ankle jerks were absent. Sensation to cotton wool and pinprick was impaired over both forearms and legs, and also over the front of the chest and lumbar region. The urine contained no albumen or sugar.

X-ray (Fig. 1 A) showed considerable broadening of the heart shadow to the left and right, and the left contour suggested enlargement of the left ventricle. The hilar shadows were unduly stressed, as were also the vascular markings in the lung fields. Four examinations of the sputum were negative for tubercle bacilli. Wassermann and Kahn reactions were negative.

A fractional test meal showed complete achlorhydria, and the same test repeated after histamine injection showed absence of hydrochloric acid except in two samples, which were neutralized by 10 c.c. of N/10 NaOH.

*Progress.*—The patient was kept at rest in bed on a restricted salt and fluid intake; his alcohol was stopped, and a diet adequate in vitamin B<sub>1</sub>, containing two eggs per diem, was given. The dyspnœa and œdema decreased. The enlargement of the heart disappeared within a month, and still further reduction had taken place three months later (Fig. 1 B). The pulse rate, which was at first 120, declined to 80 in eight days.

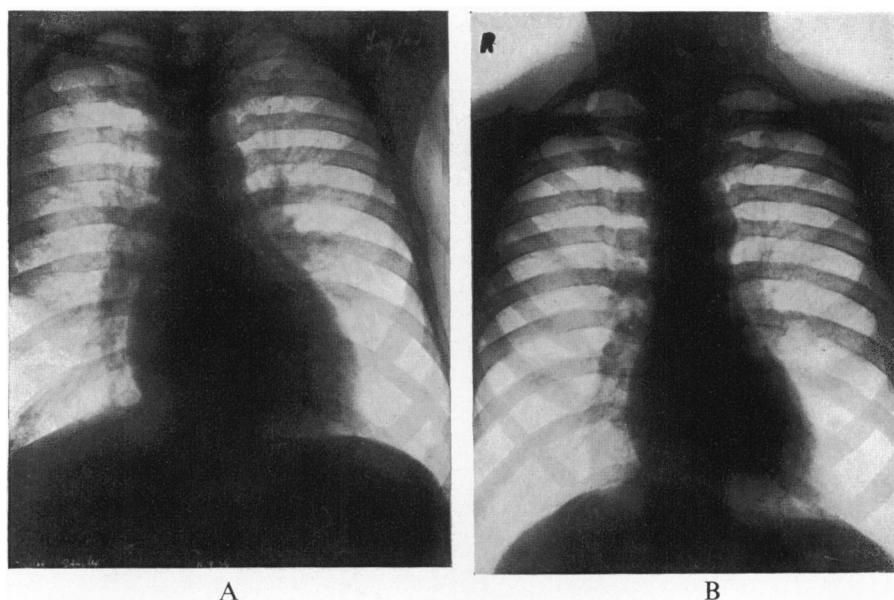


FIG. 1.—Case 1. Radiograms before and after treatment.

(A) September 11. The transverse diameter of the heart is much increased to the right and left ; considerable pulmonary congestion is present.

On September 22 the transverse diameter of the heart has considerably diminished (by 2·2 cm.) and the pulmonary congestion has disappeared.

(B) December 22. The transverse diameter of the heart is still further reduced, the total reduction of the transverse diameter being 3 cm.

This and the films in Fig. 2 have been taken with a standard technique, but were not teleradiograms.

The limbs, however, remained painful, tender, and weak ; and as alcoholism had probably caused the peripheral neuritis, it was decided to try vitamin B<sub>1</sub> therapy. At that time Strauss (1935) and others in America had established the identity of alcoholic peripheral neuritis with beri-beri, and Russell (1936) in Scotland had successfully treated certain cases of peripheral neuritis with vitamin B<sub>1</sub>. One of Russell's patients had clinical evidence of enlargement of the heart and " heart attacks." The possibility of the cardiovascular changes in this case being also due to beri-beri was then considered ; Weiss and Wilkins had published their findings in the same year (1936).

On October 10, 1936, daily injections of vitamin B<sub>1</sub> (500 units) were begun, and in addition marmite 3 i, t.i.d., was given orally. In 11 days the injections were reduced to one on alternate days. By this time considerable subjective improvement had occurred : the appetite returned ; there was no dyspnoea or œdema, and the liver was only just palpable ; the pains in his limbs had disappeared and the muscles were less tender. Motor power took longer to recover, but on his discharge from hospital, in November, he no longer had foot drop and the power of his arms had recovered ; the knee and the left ankle jerks had returned, but were sluggish ; the right ankle jerk was still absent.

When seen in January both knee jerks and ankle jerks were brisk. He was walking well, and there was no tenderness of the calves.

## CASE 2. BERI-BERI AND SUB-SCURVY WITH MALNUTRITION AND ACHLORHYDRIA

A metal dealer, aged 42, came to hospital on May 27, 1938. Owing to bad trade he had been on a poor diet, mainly bread and margarine, though once or twice a week he would have corned beef and a little vegetable; he took no eggs, salads, or fruit; he was a teetotaller. His ankles had begun to swell 18 months before, and a week before coming to hospital increasing shortness of breath was noted—even on talking. For five days he had noticed weakness and numbness of both legs. He also complained of swelling of the gums, looseness of the teeth, and intermittent attacks of epigastric pain, relieved by vomiting.

He was thin and dyspnoëic, and pitting œdema extended up to the knees. The gums were spongy and bled easily. The cervical veins were slightly engorged, but there was no orthopnoëa.

The pulse was 110 and regular. The radial, brachial, and retinal arteries were normal for his age, and the blood pressure was 120/80. The apex beat was in the mid-clavicular line and the heart sounds were normal. No abnormal physical signs were detected over the lungs or in the abdomen. Motor power in the legs was moderately impaired. The knee jerks were present, but the ankle jerks were difficult to elicit. The calves were somewhat wasted and tender; objectively sensation was not impaired to cotton wool or pinprick over the lower limbs.

The heart was enlarged to the left and right, and there was evidence of pulmonary congestion in the hilar and basal regions (Fig. 2A).

No tubercle bacilli were found in the sputum. The fractional test meal, with and without histamine, showed complete achlorhydria. The blood count showed no anæmia and no abnormality. The Wassermann reaction was negative. The specific gravity of the urine was 1022 and there was no albumin or sugar.

*Progress.*—The patient was kept at rest in bed on an ordinary hospital diet containing fruit juices for five days, whilst investigations were being made, including the estimation of the vitamin B<sub>1</sub> in the blood. As this was found to be very low (2.5 µg per 100 c.c. blood), he was then given 2 mg. of vitamin B<sub>1</sub> (Benerva-Roche) by intramuscular injection daily for 18 days, after which the injections were continued on alternate days for five weeks and then twice a week for another two months. During this latter period 2 mg. of aneurin were given daily in the form of Benerva tablets. Marmite 3 i, t.i.d., was given for four weeks.

He improved steadily, the dyspnoëa disappearing in one week and the œdema in a fortnight. The pulse rate fell from 110 to 80, and the transverse diameter of the heart, as seen in the radiogram (Fig. 2B), showed a considerable decrease in 17 days. The vascular congestion in the hilar and basal regions of the lungs had also disappeared.

Unfortunately an electrocardiogram was not taken until 18 days after beginning vitamin B<sub>1</sub> therapy. It showed an inverted T in lead III, and this had become flat a month later.

On discharge from hospital in July he was feeling well and the gums no longer bled. The weakness of his legs and the tenderness of his calves had

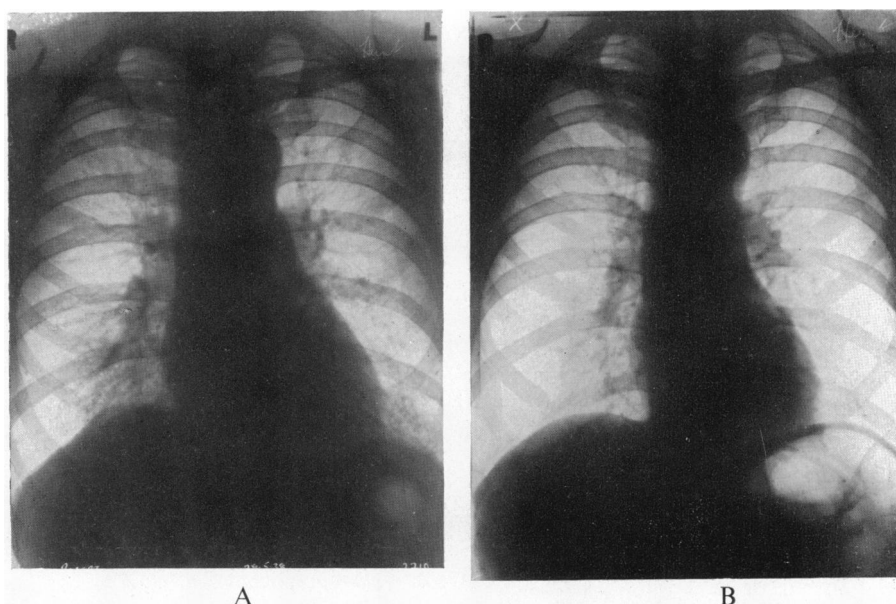


FIG. 2.—Case 2. Radiograms before and after treatment.

(A) May 28. The transverse diameter of the heart is increased, with pulmonary congestion.

(B) June 14. Reduction of transverse diameter of heart. The evidence of pulmonary congestion has disappeared.

disappeared ; the ankle jerks, however, remained sluggish. Vitamin therapy was continued.

### CASE 3. BERI-BERI AND CIRRHOSIS OF THE LIVER, IN A CHRONIC ALCOHOLIC

A publican, aged 35, was first seen on March 31, 1939. For six years he had been short of breath and had been forced to give up playing games. For a year he had been tremulous and for two weeks he had complained of pains in his legs and swelling of the ankles.

His appetite had always been small and in recent weeks had deteriorated. Morning cough and vomiting had troubled him for 18 months, and for 6 months he had suffered from recurring epistaxis. He took no breakfast. He had been in the habit of drinking 10 pints of beer and 2 or 3 ounces of whiskey, and of smoking 20 cigarettes per day. Apart from this there was nothing significant in his past history.

On examination, he was stout, and both ankles pitted on pressure. His eyes were prominent, but he asserted that they had been so ever since he could remember. There was no associated enlargement of the thyroid gland, but there was some tremor of the hands. His basal metabolic rate was later found to be +16 per cent. The exertion of getting undressed caused him to become short of breath, and the veins of the neck in the sitting position were distended up to the angle of the jaw. The pulse rate was 115 and the rhythm was regular. His arteries appeared normal for his age. The blood pressure was 130/100 mm. The apex beat could not be felt, but on percussion there was no evidence of

enlargement of the heart. A soft systolic murmur was heard over the base of the heart.

No adventitious sounds were heard over the lungs. The abdomen was prominent, and the rounded lower border of the liver could be felt five finger-breadths below the costal margin; the surface felt rough and firm in consistency. The calves were tender, the left knee jerk was more sluggish than the right. The ankle jerks were absent. Sensation to cotton wool and pinprick was diminished on the medial side of both legs and ankles.

A teloradiogram showed a high position of the diaphragm. The heart was in the horizontal position, but did not appear to be enlarged. There was evidence of pulmonary vascular engorgement. The specific gravity of the urine was 1020 and there was no sugar and no albumin.

Pending further investigations, he was advised to continue with the same diet and intake of alcohol, and he was admitted to the West London Hospital on April 4. The vitamin B<sub>1</sub> content of the blood was found to be very low (1.5 µg. per 100 c.c.).

Estimation of ascorbic acid in urine: volume 75 c.c.; 2.8 mg. per 100 c.c.; total acid 2.1 mg.

A fractional test meal showed absence of free hydrochloric acid until the last two specimens, taken at 90 and 120 minutes, the highest reading being equivalent to 25 c.c. N/10 NaOH.

*Progress.*—His intake of alcohol was then stopped. Marmite 3 i, t.i.d., was given by mouth, and also injections of 1000 units of vitamin B<sub>1</sub> (Benerva) were given on alternate days, and eleven days later daily.

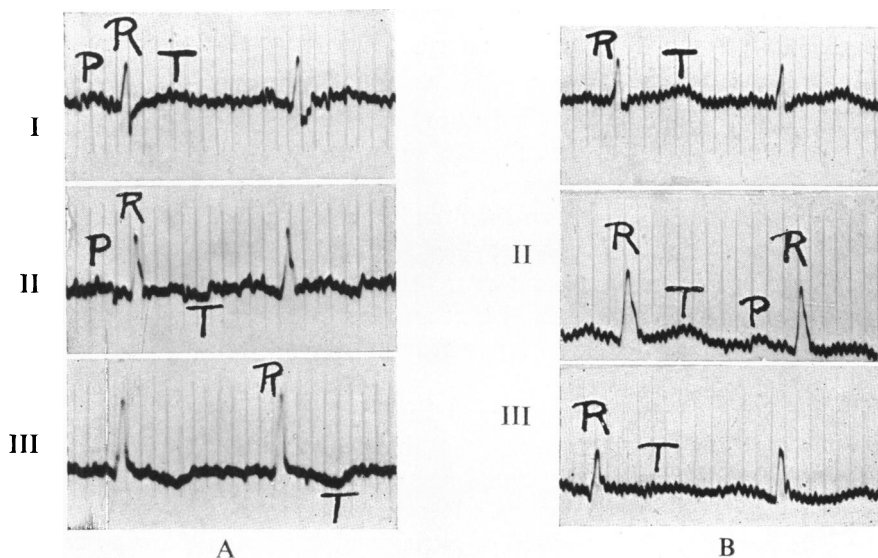


FIG. 3.—Case 3. Electrocardiograms. Time intervals 0.05 sec. Standard calibration.

(A) April 14. Sinus tachycardia, rate 100. T<sub>2</sub> and T<sub>3</sub> are negative.

(B) May 25. T<sub>2</sub> is now positive. T<sub>3</sub> is flat. T<sub>1</sub> is higher voltage. The tendency to right axis deviation has disappeared (see page 237).

The œdema and engorgement of the cervical veins disappeared at the end of two weeks. The pulse rate remained raised, averaging about 98. The liver decreased in size, and its lower border could only be felt three finger-breadths below the costal margin, two weeks after his admission; the size then remained unaltered, and the firmness of the organ gave the impression of cirrhosis. The pains in the legs and the hypoalgesia took about a month to disappear. On discharge from hospital in May the knee jerks were rather more brisk, but the ankle jerks remained absent. The vitamin B<sub>1</sub> content of the blood had risen to the normal figure of 8.5 µg. per 100 c.c.

A cardiogram taken on March 31 showed an inverted T in lead III and another on April 14 (Fig. 3A) showed a tendency to right axis deviation, with a negative T wave in leads II and III. Another taken on May 2 showed that the axis deviation had disappeared; T in lead II was now flat, but T in lead III remained negative. On May 25, T in lead II had become positive, whilst T in lead III had become flat (Fig. 3B).

X-ray repeated on May 19 showed disappearance of the pulmonary vascular congestion; the transverse diameter of the heart was almost unaltered, but the diaphragm was lower.

#### DISCUSSION

Certain features are common to these three cases. All complained of dyspnœa and of swelling of the legs; all had mild neuritis in the legs with tender calf muscles; all had tachycardia and achlorhydria (or marked hypochlorhydria). Two gave a history of chronic alcoholism and had enlarged livers; two had enlarged hearts with venous congestion but without albuminuria, hypertension, arteriosclerosis, signs of syphilis, or a history of rheumatic fever. Vitamin B<sub>1</sub> was estimated in the blood of two and found to be very low in amount; all three improved after therapy with vitamin B<sub>1</sub>.

It is customary, following Aalsmeer and Wenckebach (1929), to describe three forms of cardiac change due to deficiency of vitamin B<sub>1</sub>: first, a mild form occurring in ambulatory patients and accompanied by dyspnœa, palpitation, tachycardia, and slight dilatation of the right side of the heart; secondly, a moderately severe form accompanied by œdema, mild polyneuritis, and enlarged heart and liver and spleen; thirdly, an acute pernicious form (*shôshin*) accompanied by sudden congestive failure, præcordial distress localized to the sternum, extreme dyspnœa, and a greatly dilated heart. While the term "beriberi heart" is ascribed to any of these three forms, deficiency of vitamin B<sub>1</sub> can cause either neuritis without any cardiovascular disturbance or œdema without any obvious disturbance of the heart. We are not here concerned with the ætiology of famine œdema, which is probably usually due to dietary deficiency of protein. Schittenhelm and Schlecht (1919), in an outbreak in a German labour corps, attributed the œdema to the low protein and high salt content of the diet, and failed to cure it with vitamin B. On the other hand, Jansen (1920) found that the protein intake was not abnormally low in another series of cases in Germany. Whereas famine œdema is typically accompanied by a decrease in the plasma albumin and bradycardia or no cardiac disturbance

in wet beri-beri the plasma albumin is usually normal and cardiac disturbances (including tachycardia) are very frequent. The three cases described here belong to the moderately severe type of cardiac disturbance, although in one there was no evidence of cardiac enlargement.

The diagnosis in these cases rests upon four features : the clinical characteristics, the dietetic evidence of deficiency of vitamin B<sub>1</sub>, the response to therapy, and the estimation of the vitamin in the blood.

#### *Clinical Characteristics*

The commonest cardiac symptoms of deficiency of vitamin B<sub>1</sub> are dyspnoea on exertion, palpitation, and tachycardia. Œdema, gallop or "tic-tac" rhythm of the heart, and "pistol shots" heard over the peripheral arteries are common. The last sign, like the decreased circulation time, is due to the widespread peripheral arteriolar dilatation and is only found associated with congestive heart failure in deficiency of vitamin B<sub>1</sub>, in Graves' disease, and in fevers. The presence of most of these features in our three cases and the absence of evidence of other forms of organic heart disease suggest the diagnosis.

Following Wenckebach and Aalsmeer, whose cases were observed in the Orient, there has been a tendency to speak of right-sided failure. In the United States and in England there has been no uniformity of the clinical picture. The failure may be peripheral, or if central is often right- and left-sided ; the pulmonary vascular congestion in Cases 1 and 2 (Figs. 1 and 2) demonstrates the left ventricular stress.

The heart may be normal in size or much enlarged. Diuresis, reduction in the tachycardia, and often a hyperactive carotid sinus reflex are early signs of improvement. The rapid reduction in the transverse diameter of the heart is well seen in Figs. 1-2, and is comparable to that which occurs in the myxœdema heart when it is responding to thyroid medication. The peripheral neuritis responds less dramatically to vitamin B<sub>1</sub> therapy ; subjective improvement occurs early, but the signs usually take many weeks to disappear.

*Electrocardiographic Changes.*—Aalsmeer and Wenckebach (1928) and Wenckebach (1934) noted shortening of the P-R interval (0.12 sec. or less) in inhabitants of Java suffering from beri-beri. Other observers, notably Keefer (1930) in China and Weiss and Wilkins (1937) in the United States, have analysed series of cardiograms in beri-beri subjects. Feil (1936) reported on 38 cases of pellagra, but noted that the cardiographic changes were similar to those occurring in beri-beri ; possibly due to associated beri-beri. The chief abnormalities were sinus tachycardia, flattening or negativity of the T waves, prolongation of the Q-T interval (electrical systole), low voltage QRS waves, ventricular or auricular extrasystoles, and changes in the electrical axis either to the right or left. Mainzer and Krause (1940) also reported on 23 pellagrins, in about three fifths of whom the cardiograms were abnormal ; although the changes were similar to those in beri-beri, they emphasized the return to normal in some cases subsequent to nicotinic acid treatment : there was, however, no mention of the vitamin B<sub>1</sub> content of the hospital diet.



Electrocardiograms were not taken in Cases 1 and 2 until four and three weeks after admission to hospital, and by this time no striking changes were present. Case 3 showed sinus tachycardia, transient tendency to right axis deviation, and negative T waves in leads II and III.

Dustin *et al.* (1939) have called attention to the increasing abnormality of the cardiograms in some cases during the first week or two of treatment. Case 3 showed this interesting sequence of events ; in the first cardiogram, taken on March 31 (not reproduced here), there were no T wave changes or axis deviation, although subsequent curves showed them (Fig. 3).

*Dietetic Evidence. The Cause of Deficiency of Vitamin B<sub>1</sub>*

This has been discussed at length elsewhere (Sinclair, 1939, *a*). The requirement of the vitamin varies directly with the metabolism of the body and the ingestion of carbohydrate (or alcohol) (Cowgill, 1934) ; for this reason inanition alone does not produce deficiency. Deficiency is therefore commonest in young male adults ; particularly those who ingest large amounts of carbohydrate or of alcohol. These three patients were males aged between 35 and 42 years ; two of them gave a history of chronic alcoholism, and the diet of the third consisted mainly of bread and margarine ; all three lived on diets that were deficient in vitamin B<sub>1</sub>. If severe neuritis limits the patient's activity, cardiac disturbances are less likely : in two of the cases the neuritis was slight, and the third was at work although he could only walk with the aid of sticks. Deficiency of vitamin B<sub>1</sub> tends to occur in those with gastric achlorhydria because the vitamin is easily destroyed in an alkaline medium (there is no evidence that the deficiency causes achlorhydria) : all these three had achlorhydria or marked hypochlorhydria. Further, there is evidence that liver damage impairs the utilization of vitamin B<sub>1</sub> because the liver is the main site of phosphorylation of the vitamin : two of these patients had enlarged livers. These factors provided adequate causes for a deficiency of vitamin B<sub>1</sub>.

*Response to Therapy*

All three cases responded convincingly to therapy with vitamin B<sub>1</sub>. It is obvious that the effect of therapy was not controlled : the patients were rested in bed and given an adequate diet without alcohol and containing marmite. Case 1, however, made much quicker progress to full recovery as soon as vitamin B<sub>1</sub> was administered parenterally (and marmite orally) ; Case 2 was kept on a hospital diet for five days before the vitamin was administered parenterally. The importance of parenteral administration of the vitamin, particularly in cases with achlorhydria, was shown by the case published by Laurent and Sinclair (1938), in which large amounts of the vitamin by mouth failed to cure the neuritis or raise the blood vitamin to normal. There can be little doubt that in the three cases described above full removal of the cardiac and neuritic symptoms was due to therapy with vitamin B<sub>1</sub>. Since vitamin deficiencies are almost always multiple, controlled therapy is seldom justified, and any associated deficiency state such as pellagra, scurvy, or anæmia should receive appropriate treatment.

*Vitamin B<sub>1</sub> in the Blood*

In two of the cases the amount of vitamin B<sub>1</sub> in the blood was estimated by the modification of Meiklejohn's method recently described (Sinclair, 1939, *b*) ; a value of 4.5 µg. per 100 c.c. or less is significantly low. Very low values (1.5 and 2.5 µg. per 100 c.c.) were found in the two cases before treatment, and a normal value (8.5 µg.) was found in one case after treatment. There is a direct correlation between the amount of vitamin B<sub>1</sub> and the red cell count in the blood (Goodhart and Sinclair, 1940), but in the cases described in this paper the cell count was within normal limits. There is no doubt, therefore, that these two patients were grossly deficient in vitamin B<sub>1</sub>. This fact, combined with the evidence presented above, strongly suggests that the cardiovascular disturbances in these three patients were caused by deficiency of vitamin B<sub>1</sub>.

## SUMMARY

1. Three cases of cardiovascular disturbances caused by deficiency of vitamin B<sub>1</sub>, all living in Greater London, have been reported.
2. In two the diagnosis was confirmed by finding a very low amount of vitamin B<sub>1</sub> in the blood ; in the third no vitamin estimation was done.
3. Two of the patients were chronic alcoholics, and in one of these cirrhosis of the liver was present. The third lived on a very poor diet with a relatively high carbohydrate content. All three suffered from peripheral neuritis.
4. Achlorhydria or hypochlorhydria was present in all the cases.
5. The diagnosis, the reaction to treatment, the influence of diet and alcohol, and other associated factors have been discussed.

We are indebted for pathological investigations, apart from the vitamin B<sub>1</sub> estimations, to Dr. H. Bonnell for Cases 1 and 2, to Dr. R. G. L. Waller for Case 3, and to Dr. H. E. Archer for the basal metabolic rate and ascorbic acid estimation in Case 3. Thanks are also due to Dr. J. R. Wylie for X-rays in Cases 1 and 2.

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